

## **REMARKS**

### **Amendments to the Specification and Substitute Sequence Listing**

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is an electronic CRF copy of the Substitute Sequence Listing. The electronic CRF copy of the Substitute Sequence Listing, file "2009-11-22 0425-1257PUS1\_ST25.txt", is identical to the paper copy, except that it lacks formatting. In no way does the paper copy or the electronic CRF copy of the Substitute Sequence Listing introduce new matter into the application.

The specification is amended to properly identify the disclosed sequences with their corresponding sequence identification number (SEQ ID NO). The Sequence Listing has been updated to correct matters of form. No new matter is introduced by these amendments.

### **Status of the Claims**

Claims 1, 3-6, 12, and 14-31 are pending in the present application. Claims 3, 6-16, and 24-31 are withdrawn from consideration. Claims 2, 7-11, and 13 were previously canceled. Claims 1, 18, 20, 22, and 24-31 are amended to specify the sequences identifiers corresponding to those in the substitute sequence listing. No new matter is entered by way of these amendments. In addition, since the amendments are merely to correct sequence identifiers, no new issues are introduced by these amendments. Accordingly, entry is respectfully requested. In view of the following remarks, reconsideration is requested.

### **Substance of the Interview**

Applicants and Applicants' representative thank the Examiner for extending the courtesy of a telephone interview on November 18, 2009. Applicants' representative requested clarification of the rejection of claims 18 and 20 in the instant Office Action. The Examiner

indicated that the rejection was based upon an improper sequence listing format. That is, claims 18 and 20 referenced SEQ ID NO: 1, which is a nucleotide sequence. The Examiner stated that she was not able to search the amino acid sequence of SEQ ID NO: 1 described in claims 18 and 20, due to the format of the sequence listing. As noted above, the sequence listing format has been corrected.

### **Issues under 35 U.S.C. §112, First Paragraph**

Claims 1, 4-5, and 21-23 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, *see Office Action*, pages 3-4. Applicants respectfully traverse.

The Examiner asserts that the present application fails to support Applicants' previously submitted arguments regarding the 70%-80% identity, which is shared among the sequences described in the present application. *See Office Action*, page 4, item 11.

Applicants reiterate that the present application discloses the PsmA, BpmA, and TpmA sequences. Accordingly, a person of ordinary skill in the art would have been able to determine from the disclosed sequences whether or not the sequences share 70% to 80% identity (homology). In view of the sequence disclosure, Applicants submit that the Examiner's allegation is unreasonable. The present application sufficiently supports Applicants' submission that the sequences disclosed in the present application are 70%-80% identical.

The Examiner further alleges that Applicants have not clearly set forth the relevance between the PsmA, BpmA, and TpmA conserved regions and the described hydroxylation activity. Accordingly, the Examiner believes that an ordinary artisan would not know how to design and modify the instant sequences by 5%-10% to obtain variants, which retain the described macrolide hydroxylating activity.

However, Applicants submit that the PsmA, BpmA, and TpmA amino acid sequences described in the present application allow an ordinary artisan to compare these sequences with known P450 enzymes, *e.g.*, *Streptomyces coelicolor* A3 (2), *Streptomyces lividans*, and *SoyC* of *Streptomyces griseus*. Accordingly, an ordinary artisan can recognize the location of the conserved regions, and design a variant based on this knowledge.

For reference, Applicants submit herewith the results of an alignment at the amino acid level of *Streptomyces coelicolor* A3 (2), *Streptomyces lividans* and SoyC of *Streptomyces griseus* and PsmA, BpmA, and TpmA, *see* Exhibit A. Each area, marked-up with a square, depicts amino acids, which are common to all genes, and which are, accordingly, important to retaining function. By arbitrarily changing non-conserved regions, *i.e.*, regions other than those marked-up with squares, a 5%-10% modified sequence variant may be designed, which retains the described 16-position hydroxylating activity.

In view of the foregoing, Applicants submit that the present application supports the 70%-80% identity of the sequences disclosed in the instant specification, as argued in the May 6, 2009, response. An ordinary artisan can readily envision those sequences having 5%-10% variation from, *e.g.*, base 1322 to base 2548 of SEQ ID NO: 1, and still retain the described 16-position hydroxylating activity. Accordingly, claims 1, 4, 5, and 21-23 are adequately supported by the present application and comply with the written description requirement.

The Examiner, further, indicates that the present application teaches that there is only a "highly possible" chance that *e.g.*, SEQ ID NO: 1, encodes a hydroxylating enzyme of the cytochrome p450 type, *see* Office Action, pages 3-4, item 9. Applicants respectfully submit that this assertion is incorrect. Applicants demonstrate in the Examples of the instant application that PsmA, BpmA, and TpmA have the described hydroxylating activity, *see, e.g.*, Example 4, page 57, Example 9, page 71, and Example 12, page 80, respectively, of the originally filed application.

Further, Applicants note that claims 22 and 23 do not specify a 16-position hydroxylating activity. Nevertheless, the Examiner rejects these claims under 35 U.S.C. § 112, first paragraph, written description, for the same reasons as claims 1, 4, and 5. Applicants submit that claims 22 and 23, as well as claims 1, 4, and 5, comply with the written description requirement, *see* Example 11 of the 2008 written description guidelines.

In view of the foregoing, the claims comply with the written description requirement. Accordingly, withdrawal of the rejection is respectfully requested.

**Issues Under 35 U.S.C. § 112, Second Paragraph**

Claims 18 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, *see Office Action*, page 6. Specifically, the Examiner states that the phrase “amino acids 1-409 of SEQ ID NO: 1” is vague since SEQ ID NO: 1 is defined as a DNA sequence and not an amino acid sequence. In addition, the Examiner states that she is unable to search the amino acids of SEQ ID NO: 1.

As noted above, the format of the sequence listing has been corrected. In addition, claims 18 and 20 are amended to specify SEQ ID NO: 2, a protein sequence. Accordingly, Applicants believe the rejection is overcome and respectfully request withdrawal.

**Claim Objections**

The Examiner objects to claims 17 and 19 as dependent on a rejected base claim. In view of the above, Applicants submit that claim 1 is allowable. Accordingly, Applicants respectfully request withdrawal of the objection.

**CONCLUSION**


In view of the above, Applicants believe that the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact L. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By  47,874  
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Enclosures: Exhibit A